Course Notes: A Crash Course on Causality – Week 5: Instrumental Variables

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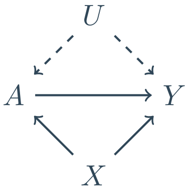
Table of Contents

Unmeasured confounding

- Suppose there are unobserved variables U that affect both A and Y, then U is an unmeasured confounding



- This violates ignorability assumption
- Since we cannot control for the unobserved confounders U and average over its distribution, if using matching or IPTW methods, the estimates of causal effects is biased
- Solution: instrumental variables

Instrumental variables

- Instrumental variables (IV): an alternative causal inference method that does not rely on the ignorability assumption

$$\begin{tikzcd} Z \arrow[r] & A \arrow[rr] & & Y \\ & & X \arrow[ul] \arrow[ur] & \end{tikzcd}$$

- Z is an IV
  - It affects treatment A, but does not directly affect the outcome Y
  - We can think of Z as encouragement (of treatement)

Example of an encouragement design

- A: smoking during pregnancy (yes/no)
- Y: birth weight
- X: mother's age, weight, etc
  - Concern: there could be unmeasured confounders
  - Challenge: it is not ethical to randomly assign smoking
- Z: randomized to either received encouragement to stop smoking ($Z = 1$) or receive usual care ($Z = 0$)
  - Causal effect of encouragement, also called intent-to-treat (ITT) effect, may be of some interest

$$E\left(Y^{Z=1}\right) - E\left(Y^{Z=0}\right)$$

  - Focus of IV methods is still causal effect of the treatment

$$E\left(Y^{A=1}\right) - E\left(Y^{A=0}\right)$$

IV is randomized

- Like the previous smoking example, sometimes IV is randomly assigned as part of the study
- Other times IV is **believed** to be randomized in nature (natural experiment). For example,
  - Mendelian randomization (?)
  - Quarter of birth
  - Geographic distance to specialty care provider

Randomized trials with noncompliance

- Setup
  - Z: **randomization** to treatment (1 treatment, 0 control)
  - A: treatment received, binary (1 treatment, 0 control)
  - Y: outcome
- Due to noncompliance, not everyone assigned treatment will actually receive the treatment, and vice verse ($A \neq Z$)
  - There can be confounding X, like common causes affecting both treatment received A and the outcome Y
  - It may be reasonable to assume that Z does not directly affect Y

$$\begin{tikzcd} Z \arrow[r] & A \arrow[rr] & & Y \\ & & X \arrow[ul] \arrow[ur] & \end{tikzcd}$$

Causal effect of assignment on receipt

- Observed data: (Z, A, Y)
- Each subject has two potential values of treatment
  - $A^{Z=1} = A^1$: value of treatment if randomized to treatment
  - $A^{Z=0} = A^0$: value of treatment if randomized to control
- Average causal effect of treatment assignment on treatment received

$$E\left(A^1 - A^0\right)$$

  - If perfect compliance, this would be 1
  - By randomization and consistency, this is estimable from the observed data

$$E\left(A^1\right) = E(A \mid Z = 1), \quad E\left(A^0\right) = E(A \mid Z = 0)$$

Causal effect of assignment on outcome

- Average causal effect of treatment assignment on the outcome

$$E\left(Y^{Z=1} - Y^{Z=0}\right)$$

  - This is intention-to-treat effect
  - If perfect compliance, this would be equal to the causal effect of treatment received
  - By randomization and consistency, this is estimable from the observed data

$$E\left(Y^{Z=1}\right) = E(Y \mid Z=1), \quad E\left(Y^{Z=0}\right) = E(Y \mid Z=0)$$

Subpopulations based on potential treatment

A^0	A^1	Label
0	0	Never-takers
0	1	Compliers
1	0	Defiers
0	0	Always-takers

- For never-takers and always-takers,
  - Encouragement does not work
  - Due to no variation in treatment received, we cannot learn anything about the effect of treatment in these two subpopulations
- For compliers, treatment received is randomized
- For defiers, treatment received is also randomized, but in the opposite way

Local average treatment effect

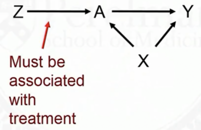
- We will focus on a local average treatment effect, i.e., the complier average causal effect (CACE)

$$
\begin{aligned}
& E\left(Y^{Z=1} \mid A^0=0, A^1=1\right)-E\left(Y^{Z=0} \mid A^0=0, A^1=1\right) \\
= & E\left(Y^{Z=1}-Y^{Z=0} \mid \text{compliers}\right) \\
= & E\left(Y^{a=1}-Y^{a=0} \mid \text{compliers}\right)
\end{aligned}
$$

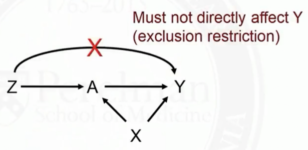
- "Local": this is a causal effect in a subpopulation
- No inference about defiers, always-takers, or never-takers

IV assumption 1: exclusion restriction

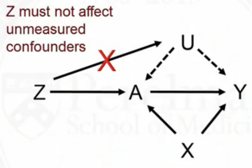
1. Z is associated with the treatment A



2. Z affects the outcome only through its effect on treatment



   – Z cannot directly, or indirectly though its effect on U, affect Y



Is the exclusion restriction assumption realistic?

- If Z is a random treatment assignment, then the exclusion restriction assumption is met
  - It should affect treatment received
  - It should not affect the outcome or unmeasured confounders
- However, it the subjects or clinicians are not blinded, knowledge of what they are assigned to could affect Y or U
- We need to examine the exclusion restriction assumption carefully for any given study

IV assumption 2: monotonicity

- Monotonicity assumption: there are no defiers
  - No one consistently does the opposite of what they are told
  - Probability of treatment should increase with more encouragement
- With monotonicity,

Z	A	A^0	A^1	Class
0	0	0	?	Never-takers or compliers
0	1	1	1	Always-takers ~~or defiers~~
1	0	0	0	Never-takers ~~or defiers~~
1	1	?	1	Always-takers or compliers

Estimate CACE: 1. rewrite the ITT effect

- Due to randomization, we can identify the ITT effect

$$E\left(Y^{z=1} - Y^{z=0}\right) = E(Y \mid Z = 1) - E(Y \mid Z = 0)$$

- Expand the first term in the above ITT effect

$$\begin{aligned} E(Y \mid Z = 1) = &E(Y \mid Z = 1, \text{always takers})P(\text{always takers} \mid Z = 1) \\ &+ E(Y \mid Z = 1, \text{never takers})P(\text{never takers} \mid Z = 1) \\ &+ E(Y \mid Z = 1, \text{compliers})P(\text{compliers} \mid Z = 1) \end{aligned}$$

- Note 1: among always takers and never takes, Z does nothing
  - $E(Y \mid Z = 1, \text{always takers}) = E(Y \mid \text{always takers}), \quad \text{etc.}$
- Note 2: by randomization,
  - $P(\text{always takers} \mid Z = 1) = P(\text{always takers}), \quad \text{etc.}$

Estimate CACE: 1. rewrite the ITT effect, cont.

- Therefore, the first term in the ITT effect is

$$\begin{aligned} E(Y \mid Z=1) = & E(Y \mid \text{always takers}) P(\text{always takers}) \\ & + E(Y \mid \text{never takers}) P(\text{never takers}) \\ & + E(Y \mid Z=1, \text{compliers}) P(\text{compliers}) \end{aligned}$$

- Similarly, the second term is

$$\begin{aligned} E(Y \mid Z=0) = & E(Y \mid \text{always takers}) P(\text{always takers}) \\ & + E(Y \mid \text{never takers}) P(\text{never takers}) \\ & + E(Y \mid Z=0, \text{compliers}) P(\text{compliers}) \end{aligned}$$

- Their difference is

$$\begin{aligned} & E(Y \mid Z=1) - E(Y \mid Z=0) \\ = & \left[E(Y \mid Z=1, \text{compliers}) - E(Y \mid Z=0, \text{compliers}) \right] P(\text{compliers}) \end{aligned}$$

Estimate CACE: 2. compute proportion of compliers

- Thus, the relationship between CACE and ITT effect is

$$\text{CACE} = \frac{E(Y \mid Z = 1) - E(Y \mid Z = 0)}{P(\text{compliers})}$$

- To compute $P(\text{compliers})$, note that
  - $E(A \mid Z = 1)$: proportion of always takers plus compliers
  - $E(A \mid Z = 0)$: proportion of always takers
- Thus the difference is

$$P(\text{compliers}) = E(A \mid Z = 1) - E(A \mid Z = 0)$$

Estimate CACE: final formula

$$\text{CACE} = \frac{E(Y \mid Z = 1) - E(Y \mid Z = 0)}{E(A \mid Z = 1) - E(A \mid Z = 0)}$$

- Numerator: ITT, causal effect of treatment assignment on the outcome
- Denominator: causal effect of treatment assignment on the treatment received
  - Denominator is between 0 and 1. Thus, CACE $\geq$ ITT
  - ITT is underestimate of CACE, because some people assigned to treatment did not take it
- If perfect compliance, CACE $=$ ITT

IVs in observational studies

- IVs can also be used in observational (non-randomized) studies
  - Z: instrument
  - A: treatment
  - Y: outcome
  - X: covariates

- Z can be thought of as encouragement
  - If binary, just encouragement yes or no
  - If continuous, a 'dose' of encouragement

- Z can be thought of as randomizers in natural experiments
  - The key challenge: think of a variable that affects Y only through A
  - Only the assumption Z affecting A can be checked with data
  - The validity of the exclusion restriction assumption rely on subject matter knowledge

Natural experiment example 1: calendar time as IV

- Rationale: sometimes treatment preferences change over a short period of time
- A: drug A vs drug B
- Z: early time period (drug A is encouraged) vs late time period (drug B is encouraged)
- Y: BMI

Natural experiment example 2: distance as IV

- Rationale: shorter distance to NICU is an encouragement
- A: delivery at high level NICU vs regular hospital
- Z: differential travel time from nearest high level NICU to nearest regular hospital
- Y: mortality

More examples of natural experiments

- Mendelian randomization: some genetic variant is associate with some behavior (e.g., alcohol use) but is assumed to not be associated with outcome of interest
- Provider preference: use treatment prescribed to previous patients as an IV for current patient
- Quarter of birth: to study causal effect of years in school on income

Ordinary least squares (OLS) fails if there is confounding

- In OLS, one important assumption is that the covariate A is independent with residuals ϵ

$$Y_i = \beta_0 + A_i\beta_1 + \epsilon_i$$

- However, if there is confounding, A and ϵ are correlated. So OLS fails.
- Two stage least squares can estimate causal effect in the instrumental variables (IV) setting

Two stage least squares (2SLS)

- Stage 1: regress A on Z

$$A_i = \alpha_0 + Z_i\alpha_1 + e_i$$

  - By randomization, Z and e are independent
- Obtain the predicted value of A given Z for each subject

$$\hat{A}_i = \hat{\alpha}_0 + Z_i\hat{\alpha}_1$$

  - $\hat{A}$ is projection of A onto the space spanned by Z
- Stage 2: regress Y on $\hat{A}$

$$Y_i = \beta_0 + \hat{A}_i\beta_1 + \epsilon_i$$

  - By exclusion restriction, Z is independent of Y given A

Interpretation of β_1 in 2SLS: the causal effect

- Consider the case where both Z and A are binary

$$\beta_1 = E\left(Y \mid \hat{A} = 1\right) - E\left(Y \mid \hat{A} = 0\right)$$

- There are two values of $\hat{A}$ in the 2nd stage model, $\hat{\alpha}_0$ and $\hat{\alpha}_0 + \hat{\alpha}_1$
  - When we go from $Z = 0$ to $Z = 1$, what we observe is going from $\hat{\alpha}_0$ to $\hat{\alpha}_0 + \hat{\alpha}_1$
  - We observe a mean difference of $\hat{E}(Y \mid Z = 1) - \hat{E}(Y \mid Z = 0)$ with a $\hat{\alpha}_1$ unit change in $\hat{A}$
- Thus, we should observe a mean difference of $\frac{\hat{E}(Y|Z=1)-\hat{E}(Y|Z=0)}{\hat{\alpha}_1}$ with 1 unit change in $\hat{A}$
- The 2SLS estimator is a consistent estimator of the CACE

$$\beta_1 = \text{CACE} = \frac{\hat{E}(Y \mid Z = 1) - \hat{E}(Y \mid Z = 0)}{\hat{E}(A \mid Z = 1) - \hat{E}(A \mid Z = 0)}$$

More general 2SLS

- 2SLS can be used
  - with covariates X, and
  - for non-binary data (e.g, a continuous instrument)
- Stage 1: regression A on Z and covariates X
  - and obtain the fitted values $\hat{A}$
- Stage 2: regress Y on $\hat{A}$ and X
  - Coefficient of $\hat{A}$ is the causal effect

Sensitivity analysis

- Sensitivity analysis method studies when each of the IV assumption (partly) fails
  - Exclusion restriction: if Z does affect Y by an amount p, would my conclusion change? Vary p
  - Monotonically: if the proportion of defiers was π, would my conclusion change?

Strength of IVs

- Depend on how well an IV predicts treatment received, we can class it as a strong instrument or a weak instrument
- For a weak instrument, encouragement barely increases the probability of treatment
- Measure the strength of an instrument: estimate the proportion of compliers

$$E(A \mid Z = 1) - E(A \mid Z = 0)$$

  - Alternatively, we can just use the observed proportions of treated subjects for $Z = 1$ and for $Z = 0$

Problems of weak instruments

- Suppose only 1% of the population are compliers
- Then only 1% of the samples have useful information about the treatment effect
  - This leads to large variance estimates, i.e., estimate of causal effect is unstable
  - The confidence intervals can be too wide to be useful

References

- Coursera class: “A Crash Course on Causality: Inferring Causal Effects from Observational Data”, by Jason A. Roy (University of Pennsylvania)
  - https://www.coursera.org/learn/crash-course-in-causality